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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,435	ERLANDER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.10-0.

DETAILED ACTION

1. Applicants' response to the office action filed on March 24, 2005 has been entered.

Status of the Application

2. Claims 1-21 are pending. Claim 1 is amended to include new limitation (in said captured or isolated cells). Further Claims 2 and 4 are amended to include all limitations of amended claim 1.

3. Applicants' response to the office action is fully considered and found not persuasive. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. This action is made FINAL necessitated by Amendment.

New Grounds of Rejection necessitated by Amendment

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1-7, 19, are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Am J Pathology, Vol. 152, No. 6, page 1427-1432, 1998 in view of Emmert-Buck et al. (Science, Vol. 274, No. 8, page 1-4, 1996).

Zhang et al. teach a method of claims 1-4, for detecting the presence of a ligand (carbohydrate antigen) in a cell or tissue sample (culture cells or blood cells), said method comprising,

(i) contacting said with a binding agent (antibody), attached to a detectable nucleic acid molecule (complexed with biotinylated DNA) (see page 1428, col. 2, paragraphs 1-2, page 1429, col. 1, paragraph 3);

(iv) detecting cells comprising said nucleic acid molecule bound to antibody-antigen complex and identifying the presence or absence of said nucleic acid as an indication of the presence of said ligand (antigen) (see page 1428, col. 2, paragraph 2, page 1429, col. 1, paragraph 3).

With regard to claims 1-4, Zhang et al. disclose that said binding agent is an antibody (see page 1428, col. 1, line 1-16, col. 2, paragraph 1);

With regard to claims 4-5, Zhang et al. teach that said detection is carried out using PCR and the presence of said ligand is quantitated (see page 1428, col. 2, paragraph 2, page 1429, col. 1, paragraph 3, Fig.1).

With regard to claim 19, Zhang et al. teach said ligand is a carbohydrate (see page 1427, col. 1, paragraph 1 (summary or abstract)).

However Zhang et al. did not specifically teach staining said sample of cells to identify cells of interest and capturing or isolating said cells of interest before detecting the presence of said ligand.

Emmert-Buck et al. teach a laser capture microdissection method for selective transfer and recovery of tissue samples using LCM, wherein Emmert-Buck et al. disclose tissue section fixed on glass slides are stained using histochemical staining (H & E stain) and the cells of interest were captured using laser capture microdissection (see page 2, col. 1, line 1-8, Fig. 2) before detecting the ligand by PCR (see page 2, col. 2, line 13-21).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the presence of a ligand in a manner taught by Emmert- Buck et al. using the histochemical staining for visualization of cells of interest and capturing said cells of interest to achieve expected benefit of developing a sensitive method of detecting said ligand because Emmert-Buck et al. taught that the LCM provides selective capture of pure population of cells of interest from heterogeneous tissue, faster, and minimizes contamination, particularly important for PCR-based analysis (see page 1, col. 2, paragraphs 1-2, col. 3, paragraph 1-2) . An ordinary practitioner would have been motivated to combine the method of for detecting the presence of a ligand in a cell as taught by Zhang et al. with the step of staining and capturing cells of interest for the purpose of reducing background noise of unwanted cells from heterogonous cells. The ordinary artisan would have a reasonable expectation of success that inclusion of Laser capture microdissection of cells of interest in the method taught by Zhang et al. would result in an increase in the sensitivity and specificity of the method for detecting the

presence of a ligand in a cell and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

B. Claims 1-2, 6-7, 13-15, 18-19, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eberwine (WO 98/22624) in view of Emmert-Buck et al. (Science, Vol. 274, No. 8, page 1-4, 1996).

Eberwine et al. teach a method of claim 1, 18-19, for detecting the presence of a ligand (protein) in cell sample comprising: (a) contacting said sample with a binding agent (antibody) attached to a detectable nucleic acid molecule (complexed with a RNA promoter driven cDNA sequence) (see page 6, line 3-31; (c) detecting said detectable nucleic acid as an indication of the presence of said ligand (see page 6, line 20-31).

With regard to claim 2, 21, Eberwine et al. teach that the binding agent is an antibody (see page 6, line 4-20);

With regard to claim 19, Eberwine et al. teach that said ligand is a protein (see page 6, line 5-6);

With regard to claims 13-15, Eberwine et al. teach said nucleic acid molecule comprises a T7 promoter and detecting said ligand comprises contacting said promoter with T7 polymerase and identifying transcription initiated from said T7 promoter (see page 7, line 20-29);

However, Eberwine et al. did not teach staining and capturing or isolating stained cells before detecting cells of interest before detecting said ligand.

Emmert-Buck et al. teach a laser capture microdissection method for selective transfer and recovery of tissue samples using LCM, wherein Emmert-Buck et al. disclose tissue section fixed on glass slides are stained using histochemical staining (H & E stain) and the cells of

interest were captured using laser capture microdissection (see page 2, col. 1, line 1-8, Fig. 2) before detecting the ligand (see page 2, col. 2, line 13-21).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the presence of a ligand in a manner taught by Emmert- Buck et al. using the histochemical staining for visualization of cells of interest and capturing said cells of interest to achieve expected benefit of developing a sensitive method of detecting said ligand because Emmert-Buck et al. taught that the LCM provides selective capture of pure population of cells of interest from heterogeneous tissue, faster, and minimizes contamination, particularly important for PCR-based analysis (see page 1, col. 2, paragraphs 1-2, col. 3, paragraph 1-2) . An ordinary practitioner would have been motivated to combine the method of for detecting the presence of a ligand in a cell as taught by Eberwine et al. with the step of staining and capturing cells of interest for the purpose of reducing background noise of unwanted cells from heterogonous cells. The ordinary artisan would have a reasonable expectation of success that inclusion of Laser capture microdissection of cells of interest in the method taught by Eberwine et al. would result in an increase in the sensitivity and specificity of the method for detecting the presence of a ligand in a cell and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

C. Claims 8-9, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Am J Pathology, Vol. 152, No. 6, page 1427-1432, 1998) in view of Emmert-Buck et al. (Science, Vol. 274, No. 8, page 1-4, 1996) as applied to claim 1-7, 19 above, and further in view of Oku et al. (USPN. 5,789,165).

Zhang et al. in view of Emmert-Buck et al. disclose the method for detecting the presence of a ligand in a cell sample as discussed in section 4A above.

Neither Zhang et al. nor Emmert-Buck et al. disclose use of multiple binding agents attached to different nucleic acid molecules to detect different ligands.

Oku et al. teach a method for detecting plurality of ligands using plurality of binding agents (antibodies) attached to different nucleic acid molecules (see col. 4, line 9-21).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the presence of plurality of ligands in a manner taught by Oku et al. et al. using the plurality of binding agents attached to different nucleic acid molecules to achieve expected benefit of developing a multiplex method of detecting Plurality of ligands in a single assay format because Oku et al. taught that use of plurality of binding agents in a single reagent provides detection of plurality of ligands in a single assay reagent (see col. 4, line 5-12). An ordinary practitioner would have been motivated to combine the method of for detecting the presence of a ligand in a cell as taught by Zhang et al. in view of Emmert-Buck et al. with the step of multiple binding agents for the purpose of analysis of multiple ligands in a cell sample. The ordinary artisan would have a reasonable expectation of success that inclusion of multiple binding agents taught by Oku et al. would result in an increase in a high-throughput assay for detecting multiple ligands and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

D. Claims 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eberwine (WO 98/22624) in view of Emmert-Buck et al. (Science, Vol. 274, No. 8, page 1-4, 1996) as

applied to claim 1-2, 13-15, 18-19, 21 above, and further in view of Oku et al. (USPN. 5,789,165).

Eberwine in view of Emmert-Buck et al. disclose the method of detecting the presence of a ligand in a cell sample as discussed in section 4B above.

Neither Eberwine nor Emmert-Buck et al. teach use of a microarray for identifying transcription products.

Oku et al. teach a method for detecting plurality of ligands in as sample, wherein Oku et al. teach identifying the ligand bound antibody-nucleic acid conjugates to nucleotides immobilized on a solid phase (microarray) and said nucleotides on the solid phase are capable of binding said products by base pair complementarity (see col. 4, line 56-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the transcription products in a manner taught by Oku et al. et al. using a microarray comprising nucleic acid molecules capable of binding to said products by base pair complementarity to achieve expected benefit of developing an enhanced specificity of the detection in a highthroughput assay format assay format because Oku et al. taught immobilized nucleotides characteristically has a high specificity that the time required for such pairing is far shorter than the time required for the formation of an antigen-antibody complex (see col. 4, line 63-67). An ordinary practitioner would have been motivated to combine the method of for detecting the presence of a ligand in a cell as taught by Eberwine et al. in view of Emmert-Buck et al. with the step of microarray based detection for the purpose to increase the specificity of detection process. The ordinary artisan would have a reasonable expectation of success that inclusion of multiple binding agents taught by Oku et al. would result in an increase specificity

of detecting ligands in a high-throughput assay and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

E. Claims 1-3, 6-12, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable Reiter et al. (Genes, Chromosomes & Cancer, Vol. 27, pp. 95-103, 2000) in view of Emmert-Buck et al. (Science, Vol. 274, No. 8, page 1-4, 1996).

Reiter et al. teach a method of claim 1, 19, for detecting the presence of a ligand (nucleic acid) in a prostate tissue sample comprising: (a) contacting said sample with a binding agent (anti-digoxigenin antibody) attached to a detectable nucleic acid molecule (digoxigenin labeled DNA probe) (see page 96, col. 2, paragraph 1-2, page 97, col.1, which indicates the detectably labeled DNA (digoxigenin labeled PSCA probe) is attached to a binding agent (anti-digoxigenin antibody)); staining said tissue sample to identify cells of interest (see page 96, col. 2, last line of paragraph 2, page 97, col. 1, line 1-2); (c) detecting said detectable nucleic acid (PSCA probe signal) as an indication of the presence of said ligand (see page 97, col. 1, paragraph 1-2).

With regard to claim 8, Reiter et al. teach plurality of agents (antibodies) are attached to a plurality of different nucleic acid molecules (PSCA, MYC probes) to detect simultaneously the plurality of ligands (PSCA and MYC specific ligands) (see page 96, col. 2, paragraph 2);

With regard to claim 2, 9, Reiter et al. teach that the binding agent is an antibody (see page 96, col. 2, paragraph 2);

With regard to claim 3, Reiter et al. teach that said sample comprises a tissue section (see page 96, col. 2, paragraph 1-2);

With regard to claim 6, Reiter et al. teach that said staining is by histochemical staining (see page 96, col. 2, last line of paragraph 2, page 97, col. 1, line 1-2);

With regard to claims 10-11, Reiter et al. teach that the sample is prostate tissue and the ligand is prostate specific ligand (see page 96, col. 1, paragraph 2, col. 2, paragraphs 1-2).

However, Reiter et al. did not teach capturing or isolating stained cells of interest before detecting said ligand.

Emmert-Buck et al. teach a method of claims 1, 7, 12, a laser capture microdissection method for selective transfer and recovery of tissue samples using LCM, wherein Emmert-Buck et al. disclose tissue section fixed on glass slides are stained using histochemical staining (H & E stain) and the cells of interest were captured using laser capture microdissection (see page 2, col. 1, line 1-8, Fig. 2) before detecting the ligand by PCR (see page 2, col. 2, line 13-21).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the presence of a ligand in a manner taught by Emmert- Buck et al. using the capturing of cells of interest identified by staining said cells to achieve expected benefit of developing a sensitive method of detecting said ligand because Emmert-Buck et al. taught that the LCM provides selective capture of pure population of cells of interest from heterogeneous tissue, which minimizes contamination (see page 1, col. 2, paragraphs 1-2, col. 3, paragraph 1-2). An ordinary practitioner would have been motivated to combine the method of for detecting the presence of a ligand in a cell as taught by Reiter et al. with the step of staining and capturing cells of interest for the purpose of reducing background noise of unwanted cells from heterogonous cells. The ordinary artisan would have a reasonable expectation of success that inclusion of Laser capture microdisection of cells of interest in the method taught by Reiter et al. would result in an increase in the sensitivity and specificity of the method for detecting the

presence of a ligand in a cell and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

F. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reiter et al. (Genes, Chromosomes & Cancer, Vol. 27, pp. 95-103, 2000) in view of Emmert-Buck et al. (Science, Vol. 274, No. 8, page 1-4, 1996) as applied to claim 1-3, 6-9, 10-12, 19 above, and further in view of Wang et al. (Biochem Biophys Res commm, Vol. 259, pp. 21-28, 1999).

Reiter et al. in view of Emmert-Buck et al. teach a method for detecting a ligand in a tissue or cell sample as discussed in section 4E above.

Neither Reiter et al. nor Emmert-Buck et al. teach that said plurality of ligands comprise two forms of a polypeptide and the two forms are the phosphorylated and unphosphorylated forms of a polypeptide.

Wang et al. teach a method for screening ligands for treatment of prostate cancer, wherein Wang et al. teach that the androgen receptor ligands stimulate androgen receptor (AR) phosphorylation, and AR phosphorylation and dephosphorylation may serve as a new molecular target for screening androgen antagonists for the treatment of prostate cancer (see page 27, col. 1, lines 1-12, page 21, abstract).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method of detecting a ligand in a tissue or cell sample as taught by Reiter et al. in view of Emmert-Buck et al. with the method of screening for two forms of a ligand as taught Wang et al to improve the detection method for the purpose of identifying the ligands that serve as drug targets for treating prostate cancer because Wang et al. explicitly taught the two forms of a polypeptide might serve as a molecular targets in identifying

ligands that are useful for prostate cancer treatment (see page 27, col. 1, lines 1-12, page 21, abstract). An ordinary practitioner would have been motivated to combine the method of Reiter et al. in view of Emmert-Buck et al. with the two forms of a ligand to achieve an improved method of detecting ligands that are useful as molecular targets for prostate cancer because an ordinary person skill in the art would have a reasonable expectation of success that the inclusion of identifying two forms of a ligand with the detection method would result in differentiating and isolating specific ligand expressing cell populations from a complex tissue that can be used for the treatment of prostate cancer.

Response to arguments:

5. With regard to the rejection under 35 USC 103(a) as being unpatentable over Reiter et al. in view of Fend et al., Applicants' arguments and amendment are fully considered and found persuasive in part. Regarding the arguments based on attacking references individually, Examiner notes that according to MPEP 2145 "One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)." However, the rejection is withdrawn in view of the amendment and new grounds of rejections.

6. With regard to the rejection under 35 USC 103(a) as being unpatentable over Eberwine et al. in view of Fend et al., Applicants' arguments are fully reviewed and found persuasive and the rejection is withdrawn in view of the amendment and arguments and new grounds of rejections.

7. With regard to the rejection under 35 USC 103(a) as being unpatentable over Reiter et al. in view of Fend et al. and in view of Wang et al. Applicants' arguments and amendment are fully

considered and found persuasive and the rejection is withdrawn in view of amendment and arguments and new grounds of rejections.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SBC
Suryaprabha Chunduru
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
5/20/05